Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1, 34-35, 38-39, 41-42, 44, 46, 52-53, and 55-68 are pending in the application, with claims 1, 34, 52, 58, and 68 being the independent claims. Claims 2-33, 40, 45, and 47-51 were previously sought to be canceled without prejudice to or disclaimer of the subject matter therein. Claims 36-37, 43, and 54 are herewith sought to be canceled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue any of the canceled subject matter in related applications. Claims 1, 34-35, 38-39, 41, 44, 46, and 52-53 are sought to be amended. Claims 55-68 are sought to be added. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Support for the amendments to claims 1, 34, and 52 is found, *inter alia*, in the specification as originally filed at page 5, lines 26-32; and page 9-10, bridging paragraph.

Support for the amendments to claims 1 and 52 is found, *inter alia*, in the specification as originally filed at page 4, lines 7-11; and page 15, lines 6-15.

Support for the amendments to claims 1, 34, and 52 is found, *inter alia*, in the specification as originally filed at page 11, lines 13-17.

Support for the amendments to claim 1, 34, and 52 is found, *inter alia*, in the specification as originally filed at pages 2-3, bridging paragraph; page 3, lines 13-19; page 8, lines 28-33; and the Examples.

Support for new claim 55 is found, *inter alia*, in the specification as originally filed at page 11, lines 13-17; page 26, lines 8-13; and Example 3.

Support for new claims 56-57 is found, *inter alia*, in the specification as originally filed at page 4, lines 19-25 and lines 33-34.

Support for new claims 58-68 is found, *inter alia*, in the previously pending claims and in the specification as originally filed at pages 2-3, bridging paragraph; page 3, lines 13-19 and lines 27-30; page 4, lines 19-25; page 5, lines 26-32; page 8, lines 28-33; page 9-10, bridging paragraph; pages 14-15, bridging paragraph; page 20-21, bridging paragraph; and the Examples.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Substance of Interview

Applicants wish to thank the Examiner for extending the courtesy of an interview on November 15, 2006. In accordance with 37 C.F.R. § 1.133(b) and MPEP § 713.04, Applicants' undersigned representative provides the following statement of the substance of the interview held with the Examiner.

Proposed claim amendments were discussed regarding the pending claims in view of the outstanding claim rejections under 35 U.S.C. § 112, first and second paragraphs, and under 35 U.S.C. § 102. The Examiner suggested that separation of the claims into one set directed to second viral vector agents and another set directed to liposome-encapsulated cytotoxic agents would aid examination. The Examiner further suggested that amending the composition claims to recite that the therapeutic first viral vector and the second viral vector agent are not conjugated should overcome the art rejection.

II. Submission of Art without an IDS

The Examiner notes that several non-patent literature articles have been cited without providing an IDS. Office Action at page 2. Applicants note that a First Supplemental IDS was filed on September 22, 2006 listing, *inter alia*, the cited non-patent articles.

III. Claim Rejections under 35 U.S.C. § 112, Second Paragraph, Clarity

Claims 38, 44, and 46 were rejected under 35 U.S.C. § 112, Second Paragraph, as allegedly lacking clarity.

The Examiner asserts that the limitations "said viral vector is an adenovirus vector" in claim 38 and "said viral vector" in claims 44 and 46 lack insufficient antecedent basis in claims 34-37. Office Action at pages 2-3.

Purely in the interests of furthering prosecution and not as an admission that the Examiner's assertions are correct, Applicants have amended the claims to recite "said first viral vector" to make clear that "said viral vector" refers to the viral vector comprising the therapeutic nucleic acid. Accordingly , Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

IV. Claim Rejections under 35 U.S.C. § 112, First Paragraph, New Matter

Claims 1, 34-36, 38-39, 41-44, 46, and 52-54 were rejected under 35 U.S.C. § 112, First Paragraph, as allegedly including new matter.

The Examiner asserts that the language introduced in the Response filed August 4, 2006 reciting "except that if said agent is identical to said first viral vector, then said

agent is administered prior to said first viral vector" allegedly constitutes new matter. Office Action at pages 3-4.

Purely in the interests of furthering prosecution and not as an admission that the Examiner's assertions are correct, Applicants have amended the claims to remove the language at issue. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

V. Claim Rejections under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 1, 34-39, 41-44, 46 and 52-54 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement.

The Examiner asserts that there is an alleged lack of written description for a "generic agent" or a "generic particle with a size of about 10-1000nm." Office Action at pages 4 and 7-9.

Applicants note that Claims 1, 38, 43, and 54 previously recited that the agent is a second viral vector rather than a generic agent. As such, Applicants understand the claims at issue to be claims 34-37, 39, 41-42, 44, and 52-53.

Regarding the Examiner's assertions alleging lack of written description for a generic agent, purely in the interests of furthering prosecution and not as an admission that the Examiner's assertions are correct, Applicants have amended the claims and added new claims to recite that the agent is a second viral vector (claims 34-35, 39, 41-42, 44, 46, 52-53, and 55-57) or a liposome-encapsulated cytotoxin (claims 58-71). Previous claim 43 has been canceled since it is now encompassed by current claim 44.

Similarly, previous claim 54 has been canceled since it is now encompassed by current claim 46.

Regarding the Examiner's assertions alleging lack of written description for a generic particulate matter agent, purely in the interests of furthering prosecution and not as an admission that the Examiner's assertions are correct, Applicants have canceled claim 37. Applicants reserve the right to pursue the subject matter of claim 37 in related applications.

Based on the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the written description rejection.

VI. Claim Rejections under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 34-39, 41-44, 46, and 52-54 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

At pages 9-10 of the Office Action, the Examiner recognizes enablement for:

(i) a method for increasing the level of a therapeutic gene product in the liver by administering: (a) a first adenoviral vector comprising a therapeutic transgene operably linked to expression control elements for expression in hepatocytes and (b) an agent that is a second adenoviral vector not comprising the transgene administered prior to or concurrently with the first vector, where the second adenoviral vector is administered by intravenous, intraperitoneal, or direct injection into the liver;

(ii) a method for increasing the level of a therapeutic gene product in the liver by administering: (a) a viral vector comprising a therapeutic transgene operably linked to expression control elements for expression in hepatocytes and (b) a liposome-

encapsulated cytotoxic agent, administered prior to or concurrently with the first vector, where the liposome-encapsulated cytotoxic agent is administered by intravenous, intraperitoneal, or direct injection into the liver;

(iii) a method for decreasing the filtration of a vector comprising a therapeutic transgene from the vascular system passing through the liver by administering: (1) (a) a first adenoviral vector comprising a therapeutic transgene and (b) an agent that is a second adenoviral vector, or (2) (a) a viral vector comprising a therapeutic transgene and (b) a known Kupffer cell cytotoxic agent administered by methods and concentrations known to selectively kill Kupffer cells; where the agent is administered prior to or concurrently with the vector comprising a therapeutic transgene, and where as a result of administration of the agent, the vector comprising a therapeutic transgene is not filtered out of the blood stream by Kupffer cells; and

(iv) a pharmaceutical composition comprising an adenovirus comprising a therapeutic transgene operably linked to expression control elements for expression in liver cells, a pharmaceutically acceptable carrier, and either a second adenoviral vector not encoding the therapeutic transgene or a cytotoxin.

The Examiner alleges lack of enablement for:

(A) use of a generic agent (Office Action at pages 10 and 12-13);

(B) use of viral vector agents of different type than the therapeutic viral vector (Office Action at page 16);

(C) administration of a generic cytotoxin that is not liposome-encapsulated (Office Action at pages 18-19);

(D) use of generic particulate matter agents (Office Action at pages 13-14);

(E) use of promoters that are not active in liver cells (Office Action at page 10); and

(F) increasing the levels of a therapeutic gene product in a tissue other than liver (Office Action at pages 11-12).

While not acquiescing to the Examiner's rejection, points (A), (C), and (D) are moot in view of amendments described *supra*.

Use of viral vector agents of different type than the therapeutic viral vector

For viral vector agents, the Examiner states that the claims encompass combinations of a therapeutic viral vector with a viral vector agent that is a different viral type, asserting that it would be undue experimentation to determine the combinations that would yield the claimed effect. Office Action at page 16. The Examiner asserts that "adenoviral particles act through natural mechanisms to enter the cells, through specific uptake via CAR and integrins," that "viral vectors that are not adenoviral [vectors] are uptaken by another mechanism, e.g., by other receptors," and that "viruses have different mechanisms of uptake." Office Action at pages 14 and 18. As such, Applicants understand the Examiner's rejection to be based on a belief that viruses do not enter Kupffer cells by non-specific uptake and that uptake of a therapeutic viral vector could be blocked only by administration of a viral vector agent that enters Kupffer cells through an identical, virus-specific mechanism.

In contrast to the Examiner's assertions, Applicants note that uptake of viral vectors by Kupffer cells has been characterized as non-specific. For example, Alemany *et al.* note that

> adenovirus clearance from blood results in a virus half-life of less than 2 min. Similar to other non-blood-borne viruses, adenovirus

> is efficiently phagocytosed by KC [Kupffer cells] and the blood clearance kinetics suggest a high capacity, **non-specific uptake**.

J. Gen. Virol. 81: 2605-2609 (2000), at page 2608, as submitted with the Information Disclosure Statement filed on February 27, 2004. Similarly, Leissner *et al.*, published the same month as Applicant's priority date, examined the effect of CAR ablation on *in vivo* tropism of adenoviral vectors, noting that the "*in vivo* biodistribution of the CAR-ablated Ad genomes was not significantly different from the wild-type Ad." *Gene Ther. 8*: 49-57 (2001), at page 54, submitted herewith as Exhibit A. Leissner *et al.* also cites an article, Zinn *et al.*, that examined hepatic capture of labeled Ad5 knob protein as compared with capture of a reticulo-endothelial system (RES)-specific radiotracer. *Id.* As summarized by Leissner *et al.*, Zinn *et al.* demonstrated that more than 80% of the labeled molecules were detected in the liver within 10 minutes after systemic administration, suggesting that "hepatic capture of these molecules was rapid and not Ad-specific." *Id.* Leissner *et al.* state that Zinn *et al.*'s findings in relation to their own *in vivo* data "would suggest that wild type as well as CAR-mutant Ad viruses would be rapidly, systematically and **aspecifically** sequestered in the liver, after i.v. injection." *Id.* at pages 54-55.

Based on Alemany *et al.*, Leissner *et al.*, and Marianneau *et al.* (as discussed at page 23 in the Response filed on January 26, 2006 and submitted therewith as Exhibit B), one of ordinary skill in the art at the time of Applicants' priority date would have understood that Kupffer cell uptake of viral vectors can occur through non-specific mechanisms. Given the latter in view of the teachings of Applicants' disclosure, one of ordinary skill in the art would have understood that a therapeutic viral vector could be

combined with a viral vector agent that is a different viral type to obtain increased levels of the therapeutic gene product.

While Applicants believe that combinations of different viral types are enabled and request that the Examiner reconsider the rejection in view of the above analysis, purely in the interests of furthering prosecution and not as an admission that the Examiner's assertions are correct, Applicants have amended the claims to recite "wherein said second viral vector is the same type as said first viral vector" (claims 1, claims 34-35, 38-39, 41-42, 44, 46, 52-53, and 55-57). Applicants reserve the right to pursue combinations of different viral vector types of therapeutic viral vectors and viral vector agents in a related application.

Use of promoters that are not active in liver cells

The Examiner states that the previously pending claims lack enablement for the use of promoters that are not active in liver cells. Office Action at pages 10 and 12. The Examiner asserts that "because the transgene expression could be increased in liver tissues, the promoter would be required to be active in the liver cells, and not another tissue-specific type promoter." Office Action at page 12.

Purely in the interests of furthering prosecution and not as an admission that the Examiner's assertions are correct, Applicants have amended the claims to recite that the promoter "functions in hepatocytes." As would be readily understood by one of ordinary skill in the art at Applicants' priority date, promoters can be selected that allow for expression in multiple tissues. Such selection would be considered routine and is supported by the Application as filed at page 5, lines 26-28, and pages 9-10, bridging paragraph.

Increasing the levels of a therapeutic gene product in a tissue other than liver

The Examiner asserts that the claims lack enablement for increased expression of a therapeutic gene product in any tissue other than liver because the claims recite that the agent reduces Kupffer cell function and not macrophage function in other tissues. Office Action at pages 11-12. The Examiner states that because any form of administration is claimed for the therapeutic viral vector, transformation of non-liver tissues could occur before the therapeutic viral vector reaches the liver. Office Action at pages 12 and 17.

While the Specification clearly requires that the therapeutic viral vector must reach the liver in order for increased expression of the therapeutic gene product to be achieved by administration of an agent that reduces Kupffer cell function, Applicants have amended the claims to specifically recite the limitations "wherein said first viral vector and said agent reach the liver following administration" and "wherein levels of said therapeutic gene product are increased by administration of said agent." As such, one of ordinary skill in the art would understand that *increased* expression of the therapeutic gene product in either liver or non-liver tissues as claimed occurs as a result of both the therapeutic viral vector and the agent reaching the liver.

In view of the reasons set forth above, Applicants respectfully request that the Examiner reconsider and withdraw the enablement rejection.

VII. Claim Rejections under 35 U.S.C. § 102 Based on U.S. 6,001,557

Claims 52-53 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. 6,001,557 (hereinafter, 'Wilson *et al.*'). Wilson teaches two adenoviral vectors conjugated to each other via a polycation sequence. Applicants respectfully traverse the Examiner's rejection as it applies to the pending claims.

In order to anticipate a claim, a single reference must teach and enable each and every element of that claim. *See* M.P.E.P. § 2131, citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987), and *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986), *cert. denied*, 482 U.S. 909, 107 S. Ct. 2490 (1987). Claim 52 as amended recites that the first viral vector and the agent "are not conjugated." In contrast, Wilson *et al.* does not teach a composition comprising a first viral vector and a second viral vector that are not conjugated, *i.e.*, that can be administered separately. Instead, Wilson *et al.* teaches a composition comprising a shuttle vector plasmid conjugated to a poly-L-lysine modified helper virus. Wilson *et al.* at column 14, lines 6-15, and claim 1. As such, Wilson *et al.* fails to teach the compositions recited in claims 52 and 53.

While the language reciting that the first viral vector and the agent "are not conjugated" is not found verbatim in the Specification, current caselaw makes clear that

> the failure of the specification to specifically mention a limitation that later appears in the claims is not a fatal one when one skilled in the art would recognize upon reading the specification that the new language reflects what the specification shows has been invented.

All Dental Prodx, LLC v. Advantage Dental Products, 309 F. 3d 774, 779 (Fed. Cir. 2002): page 779, column 2, paragraph 6, second sentence. In *All Dental Prodx*, the Federal Circuit noted that a claim limitation that required heating a thermoplastic "unidentified mass" was not found verbatim in the Specification, but that the Specification made clear that the invention did not involve heating an *identifiable* mass. *Id.*, page 779, column 2, paragraph 6, third-fifth sentences.

Like the "unidentified mass" in *All Dental Prodx*, it would be apparent to one of ordinary skill in the art upon reading Applicants' Specification that the therapeutic first viral vector and the second viral vector agent are not conjugated as described and claimed by Wilson *et al.* The viral vectors and agents described in the Specification are always separate. Furthermore, prior administration of the viral vector agent as described by Applicants' Specification logically excludes a conjugate because if the viral vector agent were conjugated to the therapeutic viral vector then it could not be administered prior to the therapeutic viral vector. As such, upon reading Applicants' Specification, one of ordinary skill in the art would understand that the second viral vector agent and the therapeutic first viral vector are discrete, non-conjugated entities. This is further supported by the Examples in which co-administration of an adenoviral agent is described in terms of titration of the dose of the adenoviral agent in comparison to a fixed dose of the therapeutic vector, which clearly describes discrete, non-conjugated viral vectors. Specification at page 26, lines 8-13 and lines 20-26.

Given the failure of Wilson *et al.* to disclose all of the elements of claims 52 and 53, Applicants respectfully request that the Examiner reconsider and withdraw the novelty rejection.

VIII. Claim Rejections under 35 U.S.C. § 102 Based on Graham et al.

Claims 1, 38, 43, and 52-54 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. 6,730,507 (hereinafter, 'Graham *et al.*'). Graham *et al.* teaches sequential administration of adenoviral vectors expressing the same transgene. Applicants respectfully traverse the Examiner's rejection as it applies to the pending claims.

Claims 1 and 52 are the independent claims from which the other rejected claims depend. Claims 1 and 52 recite administration of a therapeutic first viral vector and a second viral vector agent lacking the therapeutic nucleic acid for increasing the level of a therapeutic gene product in a subject. In contrast, Graham *et al.* does not teach *in vivo* administration of a second viral vector agent lacking the therapeutic nucleic acid in order to increase levels of a therapeutic gene product. Instead, Graham *et al.* teaches sequential *in vivo* administration of adenoviral vectors that express the same transgene but that possess different serotypes in order to bypass neutralizing antibodies that would otherwise diminish the efficacy of transgene expression. *Id.* at column 1, lines 35-39; column 3, lines 36-40 and lines 51-54; and column 5, lines 50-56. As such, Graham *et al.* fails to teach the methods and compositions recited in claims 1, 38, 43, and 52-54.

Given the failure of Graham *et al.* to disclose all of the elements of claims 1, 38, 43, and 52-54, Applicants respectfully request that the Examiner reconsider and withdraw the novelty rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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